201-14489

May 21, 2003

By Mail
Christine Todd Whitman, Administrator
US EPA
PO Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program - Test Plan Submission from HERTG
Registration Number

Dear Administrator Whitman:

The American Chemistry Council Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG) submits for review and public comment its test plan report, as well as related robust summaries, for the single chemical, "2,5-Furandione, 3-(dodecenyl)dihydro-, Reaction Products with Propylene Oxide" (CAS # 6841l-58-5) under the Environmental Protection Agency's High Production Volume (HPV) Chemical Challenge Program. The HERTG understands that there will be a 120-day review period for the test plan report and that all comments generated by or provided to EPA will be forwarded to the HERTG for consideration.

Thank you in advance for your attention to this matter. If you have any questions regarding the test plan report or the robust summaries, or HERTG's activities associated with the Challenge Program, please contact Sarah McLallen at 703-741-5607 (telephone), 703-74 l-6091 (telefax) or Sarah McLallen@americanchemistry.com (e-mail).

Sincerely yours,

Courtney M. Price
Vice President, CHEMSTAR

cc: HERTG members

HIGH PRODUCTION VOLUME (HPV)

CHALLENGE PROGRAM

TEST PLAN

For

2,5-Furandione, 3-(dodecenyl)dihydro-, Reaction Products with Propylene Oxide

Prepared by
The American Chemistry Council
Petroleum Additives Panel
Health, Environmental, and Regulatory Task Group

May 2003

LIST OF MEMBER COMPANIES IN THE HEALTH, ENVIRONMENTAL AND REGULATORY TASK GROUP

The Health, Environmental, and Regulatory Task Group (HERTG) of the American Chemistry Council Petroleum Additives Panel includes the following member companies:

B.P. plc

Chevron Oronite Company, LLC

Crompton Corporation

Ethyl Corporation

ExxonMobil Chemical Company

Ferro Corporation

Infineum

The Lubrizol Corporation

Rhein Chemie Corporation

Rhodia, Inc.

1.0 INTRODUCTION

In March 1999, the American Chemistry Council (formerly the Chemical Manufacturers Association) Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG), and its participating member companies committed to address data needs for certain chemicals listed under the Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program. This test plan follows up on that commitment.

- Specifically, this test plan sets forth how the HERTG intends to address testing information for 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide (CAS No.: 68411-58-5).

This document indicates the findings of the data review process, and sets forth a proposed test plan to satisfy parts of the required test battery for endpoints without data that would be considered adequate under the program.

EPA guidance on the HPV Challenge Program indicates that the primary purpose of the program is to encourage "the chemical industry . . . to voluntarily compile a Screening Information Data Set (SIDS) on all chemicals on the US HPV list." (EPA, "Development of Chemical Categories in the HPV Challenge Program," p. 1.

In preparing this test plan the following steps were undertaken:

Step 1: A search was conducted for relevant published and unpublished literature on 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide.

Step 2: The compiled data was evaluated for adequacy in accordance with EPA guidance.

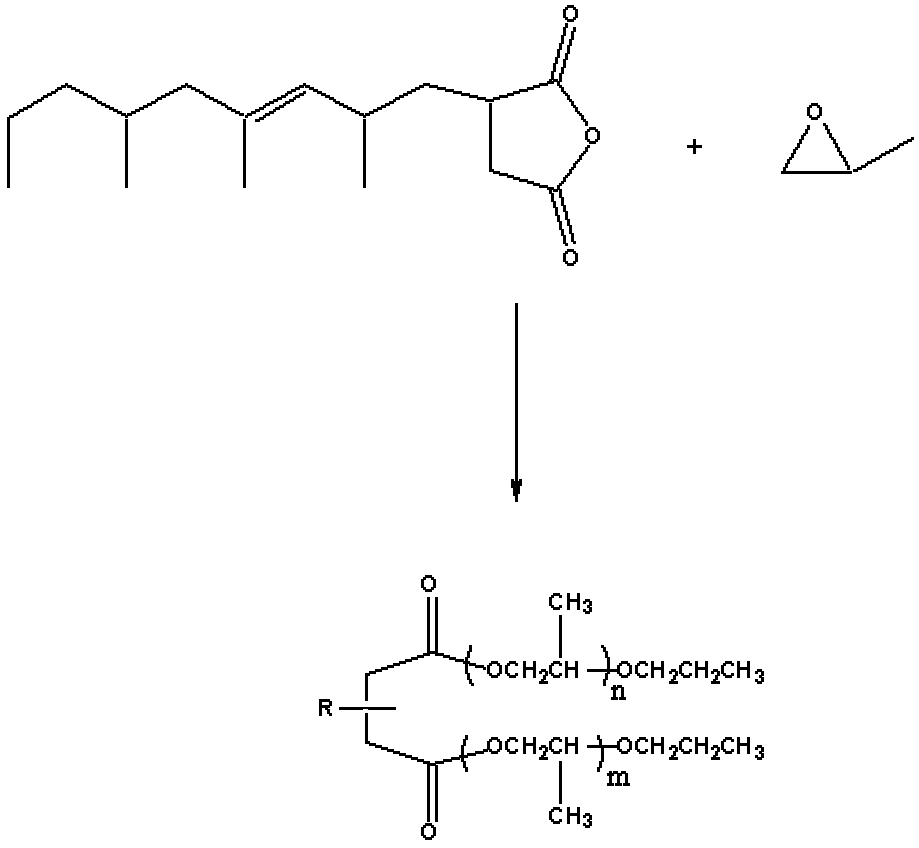
This test plan, including the following data assessment with the proposed testing scheme for the petroleum additive 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide, will be made available to EPA and to the public for review.

2.0 GENERAL SUBSTANCE INFORMATION

Chemical Name: 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide.

Chemical Abstract Service Registry Number: CAS No.: 68411-58-5

Molecular Formula: C25 H46 O7
Molecular Weight: 458.64
Structural Diagram:



Where R = dodecenyl

3.0 USE AND EXPOSURE INFORMATION

The substance 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide is commonly used as a rust inhibitor and/or surfactant in the formulation of finished lubricant additive packages including all types of internal combustion engine oils (e.g., automotive and diesel engine crankcase oils, air and water-cooled two-cycle engine oils, natural gas engine oils, marine trunk piston engine oils, medium-speed railroad diesel engine oils), automatic transmission fluids, and gear oils. This component is generally blended into finished oils where the typical concentration is less than 1 wt.% in the finished oil depending on the application.

The substance 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide is manufactured and blended into additive packages at plants owned by one or more members of the HERTG. Finished lubricants are blended at facilities owned by our customers. Additive packages are shipped to customers in bulk in ships, isocontainers, railroad tank cars, tank trucks or 55-gallon steel drums. The bulk additive packages are stored in bulk storage tanks at the customer blending sites. Finished oils are blended by pumping the lubricating oil blend stocks and the additive package from their storage tanks through computer controlled valves that meter the precise delivery of the components into a blending tank. After blending, the finished lubricant products are sold in bulk and shipped in tank trucks to large industrial users, such as manufacturing facilities and facilities that service truck fleets and passenger motor vehicles. Finished lubricants are also packaged into 55-gallon drums, 5-gallon pails, and one-gallon and one-quart containers for sale to smaller industrial users. Sales of lubricants in one-gallon and one-quart containers to consumers at service stations or retail specialty stores also occur.

Based on these uses, the potentially exposed populations include (1) workers involved in the manufacture of 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide, blending this component into additive packages, and blending the additive packages into finished lubricants; (2) quality assurance workers who sample and analyze these products to ensure that they meet specifications; (3) workers involved in the transfer and transport of 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide, additive packages or finished lubricants that contain this component; (4) mechanics who may come into contact with both fresh and used lubricants while working on engines or equipment; (5) gasoline station attendants and consumers who may periodically add lubricating oil to automotive crankcases; and (6) consumers who may change their own automotive engine oil. The most likely route of exposure for these substances is skin and eye contact. Manufacturing, quality assurance, and transportation workers will likely have access to engineering controls and wear protective clothing to eliminate exposure. Mechanics wear protective clothing, but often work without gloves or eye protection. Gasoline station attendants and consumers often work without gloves or other protective equipment. The most likely source of environmental exposure is accidental spills at manufacturing sites and during transport.

4.0 PHYSICAL CHEMICAL PROPERTIES

Physicochemical data (i.e., boiling point, vapor pressure, water solubility, and Kow) for 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide were determined using computer modeling as discussed in the EPA document titled "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program." The model used for this purpose was the EPIWIN, version 3.02[1], which was developed by the Syracuse Research Corporation. The physical/chemical properties of 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide, as determined using this computer model, are outlined in Table 1.

4.1 Molecular Weight

This substance has an average molecular weight equivalent to 458.64 gm/mol.

4.2 Melting Point and Boiling Point

2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide, as manufactured in highly refined lubricant base oil is liquid at ambient temperatures (thus melting point is not-applicable). Modeling data indicate that the boiling point of this substance is approximately 477 ^{o}C (Table 1), although this substance is likely to undergo thermal decomposition before boiling.

4.3 Vapor Pressure and Viscosity

The low volatility of this material is associated with its low vapor pressure, high viscosity, and relative high molecular weights. Modeling data indicate that the vapor pressure of 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide is approximately 5.48e-11 Pa @ 25 ^{o}C (Table 1).

4.4 Water Solubility

The water solubility of 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide is calculated as 0.035 mg/L @ 25^{o}C (Table 1). Experimental solubility data will be collected to validate the calculated results.

4.5 Octanol-Water Partition Coefficient

The log octanol-water partition coefficient (Kow) value of 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide is calculated to be 5.36

[1] Environmental Science Center- Syracuse Research Corporation- EPI for windows.

(Table 1). The octanol water partition coefficient will be determined experimentally to confirm the calculated value.

5.0 ENVIRONMENTAL FATE DATA

5.1 Physicochemical Properties Relevant to Environmental Fate

In order to understand the environmental fate of a substance, one must understand how that substance and its degradation by products partition among environmental compartments (i.e., air, soil, sediment, suspended sediment, water, and biota). The physicochemical properties of a substance influence the way in which a substance will degrade. The important environmental degradation pathways are biodegradation, hydrolysis, and photodegradation. Biodegradation is a measure of the potential of compounds to be degraded by microorganisms. Hydrolysis is a reaction in which a water molecule or hydroxide ion substitutes for another atom or group of atoms present in an organic molecule. Photodegradation is the degradation of a chemical compound as a result of absorption of solar radiation.

The physicochemical properties of the parent substance and its degradation byproducts will also influence the way in which these substances will partition among environmental compartments. Substances characterized by a low vapor pressure do not partition into air to any great extent. Similarly, substances that are characterized by low water solubility do not partition extensively into water. Substances that do not partition into air and water to any great extent tend to partition into soil and sediments.

5.2 Biodegradability

5.2.1 Test Methodologies

Chemical biodegradation involves a series of microbially-mediated reactions that may require many kinds of microorganisms acting together to degrade the parent substance. There are several standard test methods which measure primary degradation (i.e., loss of parent chemical) or ultimate degradation (i.e., complete utilization of the substance to produce carbon dioxide, water, mineral salts, and microbial biomass). Primary degradation can be determined analytically by measuring dissolved organic carbon (DOC) for water-soluble chemicals, infrared absorbance, or by a chemical-specific detection method. Ultimate degradation (also called mineralization) can be determined by measuring oxygen consumption or carbon dioxide evolution relative to the theoretical levels that can be achieved based on an elemental analysis of the chemical under investigation.

5.2.2 Summary of Available Data

Biodegradation data for 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide is summarized in Table 1.

5.2.3 Data Assessment and Test Plan for Biodegradability

A biodegradation test has been conducted on 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide according to OECD Test Guideline 301F. The results indicate 9.1% degradation after 28 days. Additional biodegradation testing is not proposed.

5.3 Hydrolysis

5.3.1 Test Methodologies

The potential for a substance to hydrolyze in water is assessed as a function of pH (OECD Guideline 111, *Hydrolysis as a Function of pH*[2]). When an organic molecule undergoes hydrolysis, a nucleophile (water or hydroxide ion) attacks an electrophile and displaces a leaving group (e.g., halogen, phenoxide).[3] Potentially hydrolyzable groups include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters[4]. The lack of a suitable leaving group renders compounds resistant to hydrolysis.

5.3.2 Summary of Available Data

The HERTG could not locate any published or unpublished hydrolysis studies of 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide.

5.3.3 Data Assessment and Test Plan for Hydrolysis

Hydrolysis (stability in water) testing, according to OECD Test Guideline 111, is proposed (Table 2).

5.4 Photodegradation

5.4.1 Test Methodologies

A prerequisite of photodegradation is the ability of one or more bonds of a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer.

The Atmospheric Oxidation Potential (AOP) of a substance can be characterized using the modeling program AOPWIN. This computer simulation is recommended in the Agency's recently released structure activity review (SAR) guidance for HPV chemicals.

5.4.2 Summary of Available Data

The HERTG could not locate any published or unpublished photodegradation studies for 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide.

[2] Organization for Economic Cooperation and Development (OECD) (1993) OECD Guidelines for Testing of Chemicals. OECD. Paris, France.
[3] W. Lyman et al. (1990) *Handbook of Chemical Estimation Methods*. Chapter 8.
[4] W.J. Lyman, W.F. Reehl, and D.H. Rosenblatt. (1982) Handbook of Chemical Property Estimation Methods. McGraw-Hill Book Co. New York, NY, USA.

5.4.3 Data Assessment and Test Plan for Photodegradation

The UV absorption of this material will be determined to evaluate if direct photodegradation will be significant. The Atmospheric Oxidation Potential (AOP) of this substance will be characterized using the modeling program AOPWIN (Table 2).

5.5 Fugacity Modeling

5.5.1 Modeling Methodologies

Fugacity-based multimedia fate modeling compares the relative distribution of chemicals among environmental compartments. A widely used model for this approach is the EQC model[5].

There are multiple levels of the EQC model. In the document, "Determining the Adequacy of Existing Data", EPA states that it accepts Level I fugacity modeling to estimate transport/distribution values. The Agency states that Level III model data are considered "more realistic and useful for estimating a chemical's fate in the environment on a regional basis". The EQC Level I model utilizes input of basic chemical properties, including molecular weight, vapor pressure, and water solubility to calculate percent distribution within a standardized environment. EQC Level III uses these parameters to evaluate chemical distribution based on discharge rates into air, water, and soil, as well as degradation rates in air, water, soil, and sediment.

5.5.2 Summary of Available Data

The HERTG could not locate any published or unpublished fugacity-based multimedia fate modeling data for 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide.

5.5.3 Test Plan for Fugacity

The relative distribution of 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide among environmental compartments will be evaluated using Level I Fugacity modeling (Table 2).

Input data to run the EQC Level I model will require an additional computer model to estimate physical/chemical properties from a structure. The model used for this purpose will be EPIWIN, version 3.02[6], which was developed by the Syracuse Research Corporation. EPIWIN includes algorithms for estimating all physical and chemical properties needed for the EQC model. The physical/chemical properties presented in Table 1 were developed using this model.

[5] Equilibrium Criterion Model- Environmental Modeling Centre as developed by D. Mackay.
[6] Environmental Science Center- Syracuse Research Corporation- EPI for windows.

6.0 ECOTOXICOLOGY DATA

6.1 Aquatic Ecotoxicity Testing

6.1.1 Test Methodologies

Acute aquatic ecotoxicity tests are usually conducted with three species that represent three trophic levels in the aquatic environment: fish, invertebrates, and algae. The fish acute toxicity test (OECD Guideline 203, *Fish, Acute Toxicity Test*) establishes the lethality of a substance to a fish during a 96-hour exposure period. The acute invertebrate test (OECD Guideline 202, *Daphnia sp., Acute Immobilization Test and Reproduction Test*) establishes the lethality of a substance to an invertebrate, typically a daphnid (*Daphnia magna*), during a 48-hour exposure period. The alga growth inhibition test (OECD Guideline 201, *Alga, Growth Inhibition Test*) establishes the potential of a substance to inhibit alga growth, typically using the freshwater unicellular green algae, *Pseudokirchneriella subcapitata* (formerly called *Selenastrum capricornutum*), during a 96-hour exposure period.

In *flow-through tests*, organisms are continually exposed to fresh chemical concentrations in each treatment level in the incoming water and there is greater assurance than with other test methods that the exposure levels and water quality remains constant throughout the test. Although flow-through testing is the preferred method, it is only applicable for chemicals that have adequate water solubility for testing.

In *static tests*, organisms are exposed in still water that is not renewed. The chemical is added to the dilution water to produce the desired test concentrations. Test organisms are then placed in the test chambers, and there is no change of water at any time during the test. There is less assurance that the test concentrations test organisms are exposed to will remain constant because test material can be adsorbed onto test chambers, degraded, volatilized, or otherwise changed during the test. Nevertheless, due to limitations of other test systems for non-volatile materials, the static test has been widely used, especially for testing organisms such as algae and *Daphnia*.

The *static-renewal test* is similar to a static test because it is conducted in still water, but the test solutions and control water are renewed periodically, usually every 24 hours. Daily test solution renewal provides a greater likelihood that the exposure concentrations will remain stable throughout the test. Daily renewals cannot be done in the algae test, and usually not in *Daphnia* tests, because the process of separation and replenishment would cause a discontinuity in the alga growth rate and it can stress, coat, or entrap *Daphnia* in any surface film during renewals. OECD considers the use of static test for fish, *Daphnia*, algae and the use of static renewal test for fish to be

appropriate for testing poorly soluble chemicals provided that test solution preparation uses water accommodated fraction or water soluble fraction methods.[7]

6.2 Aquatic Toxicity of 2,5-Furandione, 3-(dodecenyl)dihydro-, Reaction Products with Propylene Oxide

In general, the toxicity of a substance to an organism is limited by mechanisms of uptake and movement to target organs. Characteristics such as smaller molecular size and a lesser degree of ionization increase the ability of a substance to passively cross biological membranes. However, the soluble fraction of a compound in water represents the chemical fraction responsible for toxicity to aquatic organisms. Therefore, aquatic toxicity can be limited by the water solubility of a substance.

Modeling information indicates that 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide has low water solubility. The low water solubility suggests that the acute aquatic toxicity should be low due to limited bioavailability to aquatic organisms.

6.2.1 Summary of Available Data

The HERTG could not locate any published or unpublished acute aquatic toxicity data for 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide.

6.2.2 Data Assessment and Test Plan for Acute Aquatic Ecotoxicity

The HPV Challenge Program requires that data be collected on acute aquatic ecotoxicity tests in fish, invertebrates, and algae. Acute aquatic ecotoxicity testing in fish, invertebrates, and algae are proposed according to OECD Test Guidelines 203, 202 and 201, respectively (Table 2).

7.0 MAMMALIAN TOXICOLOGY DATA

7.1 Acute Mammalian Toxicity of 2,5-Furandione, 3-(dodecenyl)dihydro-, Reaction Products with Propylene Oxide

7..1.1 Acute Toxicity Test Methodology

Acute toxicity studies investigate the effect(s) of a single exposure to a relatively high dose of a substance. Oral toxicity assays are conducted by administering test material to fasted animals (typically rats or mice) in a single gavage dose.

[7] Organization for Economic Cooperation and Development (OECD) (2000). Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures. OECD Environmental Health and Safety Publications, Series on Testing and Assessment No.23, Paris, France.

Historically, lethality is a primary end-point of concern in acute toxicity studies, and the traditional index of oral potency is the median lethal dose that causes mortality in 50 percent of the test animals (LD_{50}). In addition to lethality, acute toxicity studies also provide insights regarding potential systemic toxicity through careful observation and recording of clinical signs and symptoms of toxicity as well as through detailed examination of tissues and organ systems.

7.1.2 Summary of Available Data

An acute oral toxicity study is available for 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide (Table 1).

7.1.3 Data Assessment and Test Plan for Acute Mammalian Toxicity

An adequate acute oral toxicity test was performed for 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide prior to the development of the OECD Test Guidelines. This study was considered appropriate for inclusion in this test plan. Additional acute mammalian toxicity testing is not proposed.

7.2 Mutagenicity of 2,5-Furandione, 3-(dodecenyl)dihydro-, Reaction Products with Propylene Oxide

7.2.1 Mutagenicity Test Methodology

Genetic toxicology is concerned with the effects of substances on genetic material (i.e., DNA and chromosomes). Within genetic material, the gene is the simplest functional unit composed of DNA. Mutations are generally non-lethal, heritable changes to genes which may arise spontaneously or as a consequence of xenobiotic exposure. Genetic mutations are commonly measured in bacterial and mammalian cells. The simplest test systems measure the occurrence of a base-pair substitution mutation in which a single nucleotide is changed followed by a subsequent change in the complementary nucleotide on the other DNA strand. Frame shift mutations occur following the deletion or insertion of one or more nucleotides, which then changes the “reading frame” for the remainder of the gene or multiple genes. Genetic testing for these types of point mutations is generally accomplished by *in vitro* cellular assays for forward or reverse mutations. A forward mutation occurs when there is a detectable change in native DNA whereas a reverse mutation occurs when a mutated cell is returned to its initial phenotype. Both base-pair substitutions and frame shift mutations are routinely measured in bacterial cells by measuring the ability of a cell to acquire the capability to grow in an environment missing an essential amino acid. In these tests, a large number of cells are examined to demonstrate a significant increase in the frequencies of mutations that occur over the frequency of spontaneous mutations.

Chromosomal aberrations are large scale numerical or structural alterations in eukaryotic chromosomes including deletions (visualized as breaks), translocations (exchanges), non-disjunction (aneuploidy), and mitotic recombination. Chromosomal breakage is the classical end point in chromosomal aberration assays. Substances that induce structural changes in chromosomes, especially chromosome breaks, are referred to as "clastogens." To visualize chromosomes and chromosomal aberrations following

in vitro or *in vivo* treatment with a substance, cells are arrested in metaphase, treated to swell the chromosomes, fixed, transferred to slides and stained. The first metaphase following treatment is the time at which the greatest number of cells with damaged chromosomes may be observed. The most frequently used test systems investigate changes in mammalian cells (such as Chinese hamster ovary or lung cells; human or rat lymphocytes; or human, rat or mouse bone marrow cells) following either *in vitro* or *in vivo* exposure to the test substance. The micronucleus test is a common *in vivo* assay that measures the frequency of micronuclei formation (i.e., chromosomal fragments) in polychromatic erythrocytes.

7.2.2 Summary of Mutagenicity Data

The HERTG could not locate published or unpublished mutagenicity data for 2,5 furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide.

7.2.3 Data Assessment and Test Plan for Mutagenicity Toxicity

Gene mutation and chromosomal aberration testing are proposed according to OECD Test Guidelines 471 and 474, respectively (Table 2).

7.3 Repeated-dose, Reproductive and Developmental Toxicity of 2,5-Furandione, 3-(dodecenyl)dihydro-, Reaction Products with Propylene Oxide

7.3.1 Repeated-dose Toxicity Test Methodology

Repeated-dose toxicity studies evaluate the systemic effects of repeated exposure to a chemical over a significant period of the life span of an animal (rats, rabbits, or mice). Chronic repeated-dose toxicity studies are concerned with potential adverse effects upon exposure over the greater part of an organism's life span (e.g., one to two years in rodents). Subchronic repeated-dose studies are also concerned with effects caused by exposure for an extended period, but not one that constitutes a significant portion of the expected life span. Subchronic studies are useful in identifying target organ(s), and they can be used in selecting dose levels for longer-term studies. Typically, the exposure regimen in a subchronic study involves daily exposure (at least 5 consecutive days per week) for a period of at least 28 days or up to 90 days (i.e., 4 to 13 weeks). A recovery period of two to four weeks (generally included in most study designs) following completion of the dosing or exposure period provides information on whether or not the effects seen during the exposure period are reversible upon cessation of treatment. The dose levels evaluated in repeated-dose toxicity studies are notably lower than the relatively high limit doses used in acute toxicity studies. The NOAEL (no observed adverse effect level), usually expressed in mg/kg/day, defines the dose of test material that produced no significant toxicological effects. If the test material produce toxicity at the lowest dose tested (i.e., there is no defined NOAEL), the lowest dose that produced an adverse effect is defined as the LOAEL (lowest observed adverse effect level). While these studies are designed to assess systemic toxicity, the study protocol can be modified to incorporate evaluation of potential adverse reproductive and/or developmental effects.

Reproductive and developmental toxicity studies generate information on the effects of a test substance on male and female reproductive performance such as gonadal function, mating behavior, conception, and development of the conceptus, parturition, and post-partum development of the offspring. Various study designs exist, but they all involve exposure to both male and female test animals before mating. The rat is most often selected as the test species. The test substance is administered to males and females continuously at several graduated doses for at least two weeks prior to mating and until the animals are sacrificed. The males are treated for at least two more weeks. Male gonadal histopathology is carefully assessed at the end of the study. The females are treated through parturition and early lactation. The adult females and offspring are typically studied until termination on post-natal day 21, or sometimes earlier. In addition to providing data on fertility and reproduction, this study design provides information on potential developmental toxicity following prenatal and limited post-natal exposure to the test substance. An NOAEL or LOAEL is also used to describe the results of these tests, with the exception that these values are derived from effects specific to reproduction or development.

The "toxicity to reproduction" requirement in the HPV Challenge Program can be met by conducting the *Reproduction/Developmental Toxicity Screening Test* (OECD Guideline 421) or by adding this screening test to a repeated-dose study (OECD Guideline 422, *Combined Repeated Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test*). The *One-Generation Reproduction Toxicity Study* (OECD Guideline 415) is a more comprehensive protocol for the study of the effect of a test material on reproduction and development that also meets the OECD SIDS and the HPV Challenge Program requirements.

7.3.2 Summary of Repeated-Dose Toxicity Data

The HERTG could not locate published or unpublished repeat dose, reproductive or developmental toxicity tests for 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide.

7.3.3 Data Assessment and Test Plan for Repeated-dose Toxicity

Testing is proposed in the form of OECD Test Guideline 422: A Combined Repeated Dose Toxicity Study with a Reproduction/Developmental Toxicity Screening Test (OECD 422) will be performed (Table 2).

FIGURE 1 SUMMARY TABLE OF AVAILABLE DATA

CAS No.: 68411-58-5	Study Results
Physical/Chemical Characteristics	
Melting Point	Not Applicable
Boiling Point	477 ^{O}C
Vapor Pressure	5.48E-011Pa @ 25 ^{O}C
Partition Coefficient	Log Kow = 5.36
Water Solubility	0.035 mg/L @ 25 ^{O}C
Environmental Fate	
Photodegradation	No Data Found
Hydrolysis	No Data Found
Fugacity	No Data Found
Biodegradation	9.1% @ 28 days
Ecotoxicity	
Acute Toxicity to Fish	No Data Found
Acute Toxicity to Invertebrates	No Data Found
Acute Toxicity to Algae	No Data Found
Mammalian Toxicity	
Acute Toxicity	Rat: Oral LD50 > 5 g/kg
Repeat Dose Toxicity	No Data Found
Developmental Toxicity	No Data Found
Reproductive Toxicity	No Data Found
Genetic Toxicity	
Gene Mutation	No Data Found
Chromosomal Aberration	No Data Found

FIGURE 2 Summary Table of Proposed Testing

Based on the data availability indicated in the above "Summary Table of Available Data" the following HPV Testing is proposed:

CAS No.: 68411-58-5	Testing Proposed	OECD Test Guideline Proposed
Physical/Chemical Characteristics		
Melting Point	Not Applicable	-
Boiling Point	No	-
Vapor Pressure	No	-
Partition Coefficient	Yes	OECD 107
Water Solubility	Yes	OECD 105
Environmental Fate		
Photodegradation	Yes	UV absorption & AOPWIN Model
Hydrolysis	Yes	OECD 111
Fugacity	Yes	Fugacity Level 1 Type Model
Biodegradation	No	-
Ecotoxicity		
Acute Toxicity to Fish	Yes	OECD 203
Acute Toxicity to Invertebrates	Yes	OECD 202
Acute Toxicity to Algae	Yes	OECD 201
Mammalian Toxicity		
Acute Toxicity	No	-
Repeat Dose Toxicity	Yes	OECD 422
Developmental Toxicity	Yes	OECD 422
Reproductive Toxicity	Yes	OECD 422
Genetic Toxicity		
Gene Mutation	Yes	OECD 471
Chromosomal Aberration	Yes	OECD 474

201-14489B

Substance Group: **Group 17**

Summary prepared by: **Petroleum Additives Panel**
Health & Environmental Research Task Group

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1) Melting Point

Test Substance	
CAS #	CAS# 68411-58-5
Chemical Name	2,5-Furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide
Method	
Method/Guideline followed	MPBPWIN Version 1.31 (EPIWIN)
Test Type	Boiling Point
GLP (Y/N)	Not Applicable
Year Determined	2001
Decomposition	Not Determined
Results	477.91^{O}C (Adapted Stein and Brown Method)
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the fact that this value is based on modeling rather than experimental data.
References	Unpublished confidential business information
Other	Updated: 10/10/2001

2) Vapor Pressure

Test Substance	
CAS #	CAS# 68411-58-5
Chemical Name	2,5-Furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide
Method	
Method/Guideline followed	MPBPWIN Version 1.31 (EPIWIN)
Test Type	Vapor Pressure
GLP (Y/N)	Not Applicable
Year Determined	2001
Decomposition	Not Determined
Results	5.48E-011 mm Hg @ 25 ^{O}C (Modified Grain Method)
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the fact that this value is based on modeling rather than experimental data.
References	Unpublished confidential business information
Other	Updated: 10/10/2001

3) Partition Coefficient

Test Substance	
CAS #	CAS# 68411-58-5
Chemical Name	2,5-Furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide
Method	
Method/Guideline followed	KOWWIN Version 1.65 (EPIWIN)
Test Type	Partition Coefficient
GLP (Y/N)	Not Applicable
Year Determined	2001
Results	Log Kow = 5.36
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the fact that this value is based on modeling rather than experimental data.
References	Unpublished confidential business information
Other	Updated: 10/10/2001

4) Water Solubility

Test Substance	
CAS #	CAS# 68411-58-5
Chemical Name	2,5-Furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide
Method	
Method/Guideline followed	WSKOW Version 1.36 (EPIWIN)
Test Type	Water Solubility
GLP (Y/N)	Not Applicable
Year Determined	2001
Results	0.035 mg/L @ 25 ^{O}C
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the fact that this value is based on modeling rather than experimental data.
References	Unpublished confidential business information
Other	Updated: 10/10/2001

Robust Summary - Biodegradation

Test Substance	
CAS #	68411-58-5
Chemical Name	2,5-Furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide
Remarks	This substance is referred to as 2,5-furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide in the HERTG's Test Plan for 2,5-Furandione, 3-(dodecenyl)dihydro-, Reaction Products with Propylene Oxide. For more information on the chemical, see Section 2.0 "General Substance Information" of 2,5-Furandione, 3-(dodecenyl)dihydro-, Reaction Products with Propylene Oxide in HERTG's Test Plan for 2,5-Furandione, 3-(dodecenyl)dihydro-, Reaction Products with Propylene Oxide.
Method	
Method/Guideline followed	OECD 301F
Test Type (aerobic/anaerobic)	Aerobic
GLP (Y/N)	Y
Year (Study Performed)	1999
Contact time (units)	28 days.
Inoculum	Activated sludge from domestic wastewater treatment plant.
Remarks for test conditions	Inoculum: The return activated sludge from a domestic wastewater treatment plant was used as the inoculum. The sludge was aerated and stirred for 24 hours in a flask, homogenized in a Waring blender at low/medium speed for 2 minutes, and allowed to stand for ½ to 1 hour. The supernatant was used for inoculum pre-adaptation. The sludge supernatant was supplemented with vitamin free casamino acids and yeast extracts and pre-adapted to the test material for 14 days during which the test substance was added incrementally at concentrations equivalent to 4, 8, and 8 mg carbon/L on days 0, 7, and 12, respectively. On day 14, a composite mixture was prepared by mixing equal amount of all homogenized cultures. The microbial level in the test mixture was 1000 cells/mL. Concentration of test chemical: Test substance concentration was approximately 100 mg per liter of test medium. No organic solvents were used to facilitate the dispersion of the test material. The test substance was weighed onto a Teflon coupon and introduced into the medium. Temp of incubation: 23 ± 1ºC Dosing procedure: A measured volume of the inoculated mineral medium containing approximately 100 mg/L test substance was continuously stirred in a closed system for 28 days. Sampling frequency: The oxygen uptake was monitored continuously

	and recorded every 4 hours throughout the test. Controls: Yes (blank and positive controls per guideline); abiotic and toxicity checks were not included. Sodium benzoate was used as the positive control. Analytical method: Oxygen uptake was measured using a BI-1000 electrolytic respirometer system. The system contained 2 independently controlled eight-channel reactor modules, 2 temperature controlled units, and a PC for data acquisition. Method of calculating measured concentrations: N/A Other: The inoculum was pre-adapted to the test substance for 14 days.
Results	
Degradation % after time	9.1% after 28 days
Kinetic (for sample, positive and negative controls)	Reference (sodium benzoate) – >60% (3d) Test substance – 9.1% (28d)
Breakdown Products (Y/N) If yes describe breakdown products	N
Remarks	
Conclusions	9.1% in 28 days. The reference substance, sodium benzoate, reached a level of 95.3% in the same test period.
Data Quality	(1) Reliable without restriction
References	This robust summary was prepared from an unpublished study by an individual member company of the HERTG (the underlying study contains confidential business information).
Other	Date Prepared: 10-08-01

Robust Summary – Acute Toxicity

Test Substance	
CAS #	CAS# 68411-58-5
Chemical Name	2,5-Furandione, 3-(dodecenyl)dihydro-, reaction products with propylene oxide
Remarks	Test material purity not provided.
Method	
Method/Guideline followed	Study predates OECD Guideline 401
Test Type	Acute oral toxicity
GLP (Y/N)	No, Study predates development of GLP's.
Year (Study Performed)	1962
Species/Strain	Rats/Sprague Dawley
Sex	Not specified
No. of animals/dose	Low and high dose: 2/group Mid dose 10/group.
Vehicle	None
Route of administration	Oral (intragastric)
Dose level	2, 5 and 10 g/kg
Dose volume	Not Provided
Control group	None
Chemical analysis of dosing solution	No
Remarks field for test conditions	(Note: This study was conducted prior to the establishment of this test guideline. This report provides a summary of study findings. Individual data are not presented.) A single administration of the test material was given intragastrically to adult non-fasted rats at each dose level. The animals were observed for a two-week post-dosing period.
Results	LD50 >5 g/kg
Remarks	At the 2 g/kg dose level both animals survived. At 5 g/kg 1of 10 animals died following test material administration. At the high dose (10 g/kg) 2 of 2 animals died following treatment.
Conclusions	The test article, when administered to non-fasted adult rats, had an acute oral LD50 of >5 g/kg.
Data Quality	Reliable with restriction (Klimisch Code). Restriction due to the fact that this is a summary report.
References	Unpublished confidential business information
Other	Updated: 8/30/01